The influence of fitness on exercise blood pressure and its association with cardiac structure in adolescence.

Zhengzheng Huang[1], Ricardo Fonseca,[1] James E. Sharman,[1] Chloe Park,[2] Nish Chaturvedi,[2, 3] Laura D. Howe,[4] Alun D. Hughes,[2, 3] & Martin G. Schultz.[1]

1) Menzies Institute for Medical Research, University of Tasmania, Hobart, Australia
2) Department of Population Science and Experimental Medicine, Institute of Cardiovascular Science, University College London, London, UK.
3) MRC Unit for Lifelong Health and Ageing at UCL, London, UK
4) MRC Integrative Epidemiology Unit, University of Bristol, Bristol, UK

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Corresponding author:

Dr Martin G. Schultz

Menzies Institute for Medical Research, College of Health and Medicine,

University of Tasmania, Hobart, 7000, Australia

Telephone: +61 (0) 3 6226 4264

Fax: +61 (0) 3 6226 7704

Email: Martin.Schultz@utas.edu.au

Abstract

Purpose: Exaggerated exercise blood pressure (BP) is associated with altered cardiac structure and increased cardiovascular risk. Fitness modifies these associations, but the effect in healthy adolescents is unknown. We performed an observational study to determine the influence of fitness on post-exercise BP, and on its relationship with cardiac structure in adolescents. **Methods**: 4835 adolescents from the Avon Longitudinal Study of Parents and Children, (15.4(0.3) years, 49% male) completed a submaximal cycle test. Fitness was estimated as physical work capacity 170 adjusted for lean body-mass and post-exercise BP measured immediately post-test. Cardiovascular structure and function, including left-ventricular (LV) mass (n=1589), left atrium (LA) size (n=1466), cardiac output (CO, n=1610) and total peripheral resistance (TPR, n=1610) were measured at rest by echocardiography 2.4(0.4) years later. **Results:** Post-exercise systolic BP increased step-wise by fitness tertile (131.2mmHg [130.4,132.1]; 137.3mmHg [136.5,138.0]; 142.3mmHg [141.5,143.1]). Each 5mmHg of post-exercise systolic BP was associated with 2.46g [1.91,3.01] greater LV mass, 0.02cm [0.02,0.03] greater LA size and $0.25g/m^{2.7}$ [0.14,0.36] greater LV mass index. Adjustment for fitness abolished associations (0.29g [-0.16,0.74]; 0.01cm [-0.001,0.014] and $0.08g/m^{2.7}$ [-0.001,0.002]). Similar associations between post-exercise systolic BP and each outcome were found between the lowest and highest fitness thirds. CO increased with fitness third (difference 0.06L/min [-0.05,0.17]; 0.23L/min [0.12,0.34]) while TPR decreased (difference -0.13mmHg·min/L [-0.84,0.59]; -1.08mmHg·min/L [-0.1.80,0.35]). **Conclusions:** Post-exercise systolic BP increased with fitness, which modified its association with cardiac structure. Higher CO, but lower TPR suggests a physiologically adapted cardiovascular system with greater fitness, highlighting the importance of fitness in adolescence. Abstract word count: 245.

Key words. ALSPAC, Blood Pressure, Exercise, Left Ventricle, Fitness, Adolescent

Introduction

An exaggerated blood pressure (BP) response to submaximal exercise is associated with future hypertension[1], cardiovascular events and mortality[2]. Several studies in middle-to-older age populations also indicate that raised exercise BP is associated with increased risk of left-ventricular (LV) hypertrophy[3-5], an important indicator of target organ damage and cardiovascular disease. Low cardiorespiratory fitness is also a predictor of cardiovascular disease and mortality[6-8] while increased levels of fitness improve life expectancy[9-11]. In adult populations, fitness modifies the BP response to exercise[12, 13], including its association with markers of cardiovascular disease[14, 15]. A recent study involving healthy young men found (somewhat paradoxically) evidence of a 'reverse J shape' relationship between exercise BP (recorded at any intensity of exercise) and fitness, such that exercise systolic BP was elevated in those with the highest and lowest fitness levels[16]. Nonetheless, whether exercise BP elevations in both low and high fit individuals are associated with the same level of potential cardiovascular risk remains unknown. Therefore, the aim of this study was to determine the influence of fitness on post-exercise BP, and on the post-exercise BP relationship with future cardiovascular structure and function in a large and non-selected population sample of healthy adolescents.

Materials and methods

Participants. Participants from the Avon Longitudinal Study of Parents and Children (ALSPAC), a large ongoing population-based prospective birth cohort study in UK, were selected for this analysis. Detailed descriptions of the ALSPAC design, cohort profile and examinations have been published previously[17, 18], and the study website contains details of all data available through a fully searchable data dictionary and variable search tool (http://www.bristol.ac.uk/alspac/researchers/our-data). The total sample size for analyses using any data collected after the age of seven is 15,247 pregnancies, resulting in 15,458 fetuses. Of this total sample, 14,775 were live births and 14,701 were alive at 1 year of age. The total baseline sample included in this analysis comprised 4835 adolescents who were part of the 15-year follow-up and completed a cycle exercise fitness test with post-exercise BP measurements. With no interventions, 1633 participants were followed up 2.3 ± 0.3 years later with echocardiographic assessment of cardiovascular structure and function. A flow chart of participation is outlined within supplementary figure 1. All tests were conducted conforming to the protocols approved by the ALSPAC Law and Ethics Committee and all participants (or their parent/guardian if aged < 18 years) provided informed written consent.

Exercise test and fitness assessment. All participants undertook a three-stage submaximal exercise test using an electronically braked cycle ergometer (Lode Rechor P, Groningen, the Netherlands) at baseline. This submaximal fitness test involved 9 minutes of continuous cycling at three different submaximal intensities/workloads (3×3 minute stages), individualized to each person's resting heart rate. Steady-state heart rate and workload (watts) was recorded at the last minute of each stage. The primary estimate of fitness was a predicted physical work capacity at a heart rate of 170 bpm (PWC170)[19, 20], which provides an estimate of functional/work capacity. To calculate, each heart rate and workload were plotted against each other, with a 'line of best fit' fitted through the three points and extrapolated to estimate a theoretical workload (watts) that would elicit a heart rate of 170 bpm. Some participants (n=105) did not achieve an increase in workload/heart rate with each test stage making calculation of PWC170 impossible and were excluded for this calculation. The PWC170 is known to be correlated with lean body mass[21]. This suggests fitter individuals may likely attain higher workloads relative to heart rate during the test, and would overall receive a greater exercise stimulus. To mitigate this effect, we provided a fitness estimate adjusted for lean body mass (kg) (PWC170_lm). For some analyses, the fitness measures (PWC170 and PWC170_lm) were divided into three evenly distributed tertiles from this cohort, and titled the 'lowest', 'middle' and 'highest' fitness thirds respectively.

Blood pressure. All BP measurements were taken using the validated Tango+ BP monitor (Suntech Medical, NC, USA). Participants were asked to rest for a minimum of 15 minutes prior to the measurements and fitted with an appropriately sized BP cuff (Orbit-K) before the exercise test and had two BP measurements taken in this posture (the average of which formed the pre-exercise resting BP). Whilst still wearing the BP cuff, participants were moved to an upright cycle ergometer for the exercise test. Post-exercise BP was recorded immediately on exercise cessation, with the participants remaining in an upright sitting posture on the cycle ergometer.

Cardiovascular structure and function. Cardiac structure, including LV mass, left atrial (LA) size, relative wall thickness (RWT) and cardiovascular functional measures including cardiac output (CO) and total peripheral resistance (TPR) were assessed by echocardiography. An HDI 5000 (Phillips Healthcare, North Andover, Massachusetts, USA) ultrasound with a P4-2 phased array ultrasound transducer was used for all measurements, which were undertaken at rest in the supine/left lateral position. All variable calculations were performed in compliance with the American Society of Echocardiography (ASE) guidelines[22]. Stroke volume (SV) was calculated using left ventricular end diastolic volume less LV end systolic volume, which were both calculated using the Teichholz formula[23]. SV was also indexed to body surface area (using the DuBois formula)[24] to create a stroke index (SI). Cardiac output (CO) was calculated as stroke volume × heart rate and cardiac index (CI) calculated as CO / body surface area. Total peripheral resistance (TPR) was estimated as mean arterial pressure / CO. Left ventricular (LV) mass was calculated using American Society of Echocardiography (ASE) formula[25] and was indexed to height$^{2.7}$.

Body composition, blood biochemistry maturity assessment and socioeconomic status. Height was measured to the nearest 0.1cm using a Harpenden Stadiometer and weight to the nearest 0.1 kg using a Tanita TBF 305 scales. Body mass index (BMI) was calculated by dividing weight (in kilograms) by height (in meters squared). Total fat and lean body mass were determined by a DEXA scanner (Lunar Prodigy DXA scanner; GE Medical Systems, Madison, WI, USA). Non-fasted blood was drawn and biochemistry analysis of glucose and cholesterol was undertaken following locally established procedures. A maturity offset was calculated based on the Mirwald equation[26] to assess maturation. Socioeconomic status (SES) was assigned based on paternal occupation in eight classes (1, higher managerial and professional through to 8, never worked and long-term unemployed)[27].

Statistical analysis. All analyses were conducted using Stata (version 15.0, Texas, 77845, USA, Stata Corp LLC). Numerical and visual outputs including visualization of distributions and Shapiro-Wilk test were used to screen for data normality and outliers. Multivariable linear regression was performed to determine the association between baseline post-exercise systolic BP and cardiac structure in later adolescence. Outcome variables included LV mass index, RWT and LA size, with post-exercise systolic BP input as the primary independent variable in each model. Results were presented as β coefficients (95% confidence interval, CI) per 5 mmHg increments in post-exercise systolic BP. Assumptions for linear regression were assessed by inspection of residuals and a tolerance level <0.10 was interpreted as indicating collinearity. Sex-combined models were constructed for each outcome since there was no sex*post-exercise systolic BP interaction on any of the outcomes of interest. The interaction between fitness and post-exercise systolic BP was assessed by comparing the association between post-exercise systolic BP and outcome variables (cardiac structural variables) in each tertile of fitness. Statistical interactions were defined as significant if P <0.05. Data were presented as means (95% confidence intervals) unless otherwise indicated.

Results

Demographic and clinical characteristics. Baseline characteristics of participants who received follow-up echocardiography are reported in table 1. Age, triglycerides, glucose, HDL, levels, height, pre-exercise SBP, pre-exercise DBP were quite similar in individuals across each tertile of fitness. There was a stepwise increase in male sex, weight, BMI, total lean mass, post-exercise systolic BP, peak workload and PWC170_lm, whilst cholesterol, LDL, total fat mass, pre-exercise heart rate, post-exercise DBP, post-exercise heart rate, and peak heart rate decreased with each tertile of fitness. Baseline characteristics were similar in these individuals by comparison to those in the baseline sample that did not receive follow-up echocardiography (Supplemental Table S1).

Post-exercise BP, body composition and fitness. Fitness estimated from the PWC170 and PWC170_lm was positively associated with 5 mmHg increments in post-exercise systolic BP (β=5.23 mmHg/watts 95% CI [4.83,5.63] and β=0.06 mmHg*kg/watts 95% CI [0.06-0.07] respectively). Post-exercise systolic BP increased stepwise with fitness tertile (figure 1a) while post-exercise diastolic BP remained almost the same (table 1). Both body mass index and lean body mass were correlated with fitness (PWC170) and each of the cardiac structure variables (Supplemental Table S2 and S3).

Post-exercise systolic BP and cardiac structure. There were no sex*post-exercise systolic BP interactions on any of the outcomes of interest, thus all analyses were performed on pooled data for both sexes with adjustment for sex. Each 5 mmHg increment in post-exercise systolic BP was associated with greater LV mass, LA size and LV mass index (model 1, table 2). Adjusting for age (years), sex, follow-up time (years), height (cm), maturity offset and SES attenuated the strength of relationships between post-exercise systolic BP and each outcome (model 2, table 2). When PWC170 was added into the model, post-exercise systolic BP was no longer associated with any outcome variable (model 3, table 2). Further adding lean body mass (g) and pre-exercise (resting) systolic BP (mmHg) to the models did not substantially alter the effects (model 4 and 5, table 2). Replacing PWC170 with PWC170_lm only marginally attenuated the degree of association between post-exercise systolic BP and each outcome variable (model 6, table 2). However, further adjustment for pre-exercise systolic BP (model 7) attenuated these associations. No association between post-exercise systolic BP and RWT was observed in any of the models.

The interaction of fitness and post-exercise systolic BP on cardiac structure. There was no evidence of a statistical interaction between PWC170 and post-exercise systolic BP on LV mass, LA size, RWT or LV mass index. However, as shown in figure 2 the influence of PWC170_lm on the post exercise BP-LV mass, the post exercise BP-LA size and post exercise BP-LV mass index relationships was 'U shaped', such that the coefficients were similar between the lowest and highest fitness tertiles, different to the middle tertile of fitness (figure 2). There was also evidence of borderline statistical interactions between the middle and lowest fitness tertiles for each outcome variable (Supplemental Table S4 and figures 2a, 2b, 2c) and a statistically significant interaction between the middle and highest fitness tertiles for LV mass index (Supplemental Table S4 and figure 2b). Results were broadly similar in fully adjusted models (Supplemental Table S4).

Post-exercise systolic BP, cardiovascular structure and function by fitness level. There was a step-wise increase in LV mass index with each tertile of fitness (figure 1b), along with CO (figure 1c), whilst TPR was slightly reduced with each tertile of fitness (figure 1d). However, cardiac index was similar across each tertile of fitness (2.14 ± 0.48, 2.13 ± 0.51, 2.07 ± 0.49 L/min/m^2 for PWC170 and 2.16 ± 0.50, 2.10 ± 0.51, 2.10 ± 0.47 for PWC170_lm). SV increased (49.1 ± 10.1, 54.6 ± 11.8, 61.9 ± 13.3 ml/min for PWC170 and 50.7 ± 11.3, 54.2 ± 12.3, 60.7 ± 13.0 ml/min for PWC170_lm). SI followed the same pattern and was also increased with each tertile of fitness (29.6 ± 5.8, 30.8 ± 6.4, 32.2 ± 6.6 L/min/m^2 for PWC170 and 29.7 ± 5.9, 30.3 ± 6.5, 32.6 ± 6.3 for PWC170_lm). Heart rate decreased stepwise (74 ± 10, 70 ± 10, 65 ± 10 ml/min for PWC170 and 73 ± 10, 70 ± 10, 65 ± 10 ml/min for PWC170_lm) with each tertile of fitness. Post-exercise systolic BP was associated with LV mass index, LA size and RWT in the lowest fitness (PWC170) tertile, but not within the middle and highest fitness tertiles (table 3). Post-exercise systolic BP was associated with LV mass, LV mass index and LA size in the lowest tertile of PWC170_lm (table 3). Post-exercise systolic BP was also associated with LV mass index in the highest tertile of PWC170_lm. These associations remained comparable following adjustment for sex, age (months), follow-up time (years), height (cm), SES (model 1, table 3). However, further adjustment for pre-exercise (resting) systolic BP (mmHg) attenuated these associations (model 2, table 3).

Discussion

In this cohort of adolescents, fitness was positively associated with the systolic BP response to submaximal exercise. Greater fitness and higher post-exercise systolic BP in mid-adolescence were associated with greater LV mass, LV mass index and LA size in later adolescence, and fitness accounted for the association between post-exercise systolic BP and cardiac structure. Those with greater fitness exhibited higher resting CO and lower TPR, alluding to a potentially physiologically 'adapted' cardiovascular system with higher fitness. These findings highlight the importance of considering fitness during adolescence to protect against adverse cardiovascular risk.

Low cardiorespiratory fitness is one of the most important risk factors for cardiovascular disease and mortality[28], and is associated with elevated exercise systolic BP in adult/clinical populations. A longitudinal study involving healthy middle-aged individuals indicated that those with high cardiorespiratory fitness had lower submaximal systolic BP seven years later [29]. Kokkinos *et al.* [12] reported low cardiorespiratory fitness to be associated with higher systolic

BP after 6 minutes of submaximal exercise in a group of normotensive and hypertensive females. Others have also shown lower submaximal exercise systolic BP to be independently associated with higher cardiorespiratory fitness in older adults with prehypertension[13]. However, a positive linear relationship between fitness and post-exercise systolic BP was revealed in our adolescent cohort, such that the highest post-exercise BP was achieved in those with the greatest fitness level. This is perhaps not unexpected since the major determinant of cardiorespiratory fitness (when measured as VO_{2max}) is CO[30], and a higher CO associated with greater fitness should facilitate proportionally higher exercise systolic BP, particularly at peak exercise intensity[31]. High exercise systolic BP has also been reported to be associated with high fitness at submaximal exercise intensities in young men[16]. However, whether the elevation in exercise systolic BP that is associated with high fitness shares a similar relationship with cardiovascular structure as high exercise systolic BP recorded in those with low fitness has never been determined. For the first time, our data allowed determination of the influence of fitness on the post-exercise BP-cardiac structure relationship, in a healthy young cohort in whom reverse causality is unlikely.

Post-exercise BP is likely dependant on the resting BP taken prior to exercise. However, it is relatively well-established that in older adults an exaggerated BP response to submaximal exercise (termed exercise hypertension) is associated with increased cardiovascular risk beyond resting office BP[1, 2]. Studies in adults also indicate higher exercise BP to be associated with sub-clinical disease markers including increased arterial stiffness and impaired vascular endothelial function[32], and raised left ventricular mass[14]. We recently reported pre-, post-, and recovery-submaximal exercise systolic BP to be associated with cardiovascular structure (arterial stiffness and LV mass index) independently of body composition and hypertension status in a cross-sectional analysis of adolescent participants of ALSPAC at the 17-year follow-up[33]. Despite this, few studies have specifically assessed the direct influence of fitness on the exercise systolic BP-cardiac structure relationship. We found evidence that fitness modified the post-exercise systolic BP-cardiac structure relationship, such that those with the lowest and highest fitness level shared similar positive relationships, different from that observed in the middle fitness tertile. This reveals a ‘U-shaped’ influence of fitness on the post exercise BP-cardiac structure relationship (see figure 2) and is suggestive of differential phenotypes of cardiac structure and haemodynamics underlying post-exercise BP, which are further influenced by fitness.

Elevated BP in young adults is often attributed to a hyperdynamic state in which the principal haemodynamic driver of BP is believed to be raised CO[34]. However, cross-sectional analysis of young people (mean age 17 years) from the ALSPAC cohort revealed high BP at rest to be equally associated with raised CO and TPR[35]. Altered haemodynamics at rest (i.e. elevated CO and/or TPR) may also facilitate greater BP excursions with exercise, but fitness or the habitual exercise training status of the individual may influence this[36]. Indeed, in a similar trend to both post-exercise systolic BP and LV mass index, CO increased stepwise with tertile of baseline fitness in our study. In contrast, TPR reduced stepwise. Since functional cardiovascular changes pave the way for potential cardiac structural adaptation[37, 38], our finding perhaps provides an early indication of a physiologically-adapted cardiovascular system in those with high fitness. Indeed, previous studies in athletic youth reveal differential LV structure (volume overload) and function, as result of training status and fitness.[38-40] As such, the high post-exercise BP (and to a lesser extent the greater LV mass index and LA size) found in the current study could merely be the result of optimised cardiac reserve for exercise reflected in the higher resting CO and lower TPR of the fitter individuals. Although, exercise induced adaptations to cardiac structure typically require a considerable duration and intensity of endurance exercise training stimuli[41-43], not common amongst this general adolescent population. On the other hand, we observed a similar post-exercise systolic BP-cardiac structure relationship in those with the lowest level of fitness. The least fit individuals also exhibited the highest level of resting TPR. Although the study population were apparently healthy and asymptomatic for cardiovascular disease, this could indicate a more pathological type of post-exercise BP-cardiac structure relationship present in those with poor fitness. A high TPR contributing to raised exercise afterload sustained over time could expedite negative cardiac remodelling and increase cardiovascular disease risk. However, despite these suggestions, further longitudinal studies are required to fully understand the influence of fitness on the haemodynamic nature of the exercise systolic BP-cardiac structure relationship.

Limitations

This cohort of adolescents consists predominantly of white Europeans, and our results may therefore not be applicable to other ethnic groups. The PWC170 is a submaximal exercise test that relies on extrapolation of data to derive a relative estimate of fitness. Whilst we did not have a direct measure of aerobic capacity, the PWC170 has been shown to provide reasonable predictions of VO_2 in children[44]. Moreover, the PWC170 protocol does not involve a fixed workload, and as such fitter individuals may have undertaken a greater overall exercise stimulus (i.e. attained higher workloads for a given heart rate) with potentially greater isometric muscle contraction. It is possible that this may have facilitated a greater post-exercise BP in fitter individuals. Nonetheless, our findings were largely consistent when analyses were conducted with the PWC170 normalised to lean body mass. The Teichholz method was used to calculate LV volumes, which has some limitation with respect to assumptions on chamber shape. Nonetheless, this method has shown accuracy in healthy/community-based populations.[45, 46] Our results were based on prospective epidemiological association within a largely healthy and asymptomatic cohort. As such, we were unable to identify causal relationships between fitness, post-exercise BP and cardiac structure, nor the potential (if any) for future cardiovascular risk. Although there were no interventions, since echocardiography measures were performed prospectively to the baseline exercise test, it is likely that participants may have been (or become more) recreationally active over this follow-up period or completed self-directed physical training that could have impacted some of the findings. As such, our observations require confirmation in future mechanistic and/or physiological studies.

Perspectives

Post-exercise systolic BP was associated with cardiorespiratory fitness, and cardiorespiratory fitness modified the association between post-exercise systolic BP and cardiac structure in this cohort of largely healthy adolescents. The high post-exercise systolic BP and different cardiac structure in those with higher fitness may be underpinned by a physiologically adapted cardiovascular system in which CO and TPR are better optimised in terms of cardiac reserve for exercise. Taken altogether, our findings reiterate the importance of considering fitness for cardiovascular health in adolescence. Further work is required to understand how fitness during adolescence helps to protect against adverse cardiovascular risk in the future.

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Disclosures

Declarations of interest: none.

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Figure Legends

Supplementary figure 1. Participant flow for this study.

Figure 1. Post-exercise systolic BP and echocardiographic assessment of cardiovascular structure and function at age 17 by baseline fitness. a: post-exercise systolic BP, b: left-ventricular mass index. c: cardiac output, d: total peripheral resistance. Values: are presented as mean and error bars represent 95% confidence intervals.

Figure 2. a. Per unit increase of LV mass by each 5 mmHg of post-exercise systolic BP by level of fitness (PWC170_lm). **b.** Per unit increase of LV mass index by each 5 mmHg of post-exercise systolic BP by level of fitness (PWC170_lm). **c.** Per unit increase of LA size by each 5 mmHg of post-exercise systolic BP by level of fitness (PWC170_lm). Unadjusted: unadjusted model. Adjusted: model adjusted for sex, age (months) and follow-up time (years), SES, maturity offset and height (cm). Fitness level: 1. Lowest tertile of fitness, 2. Middle tertile of fitness, 3. Highest tertile of fitness. # Statistical interaction.

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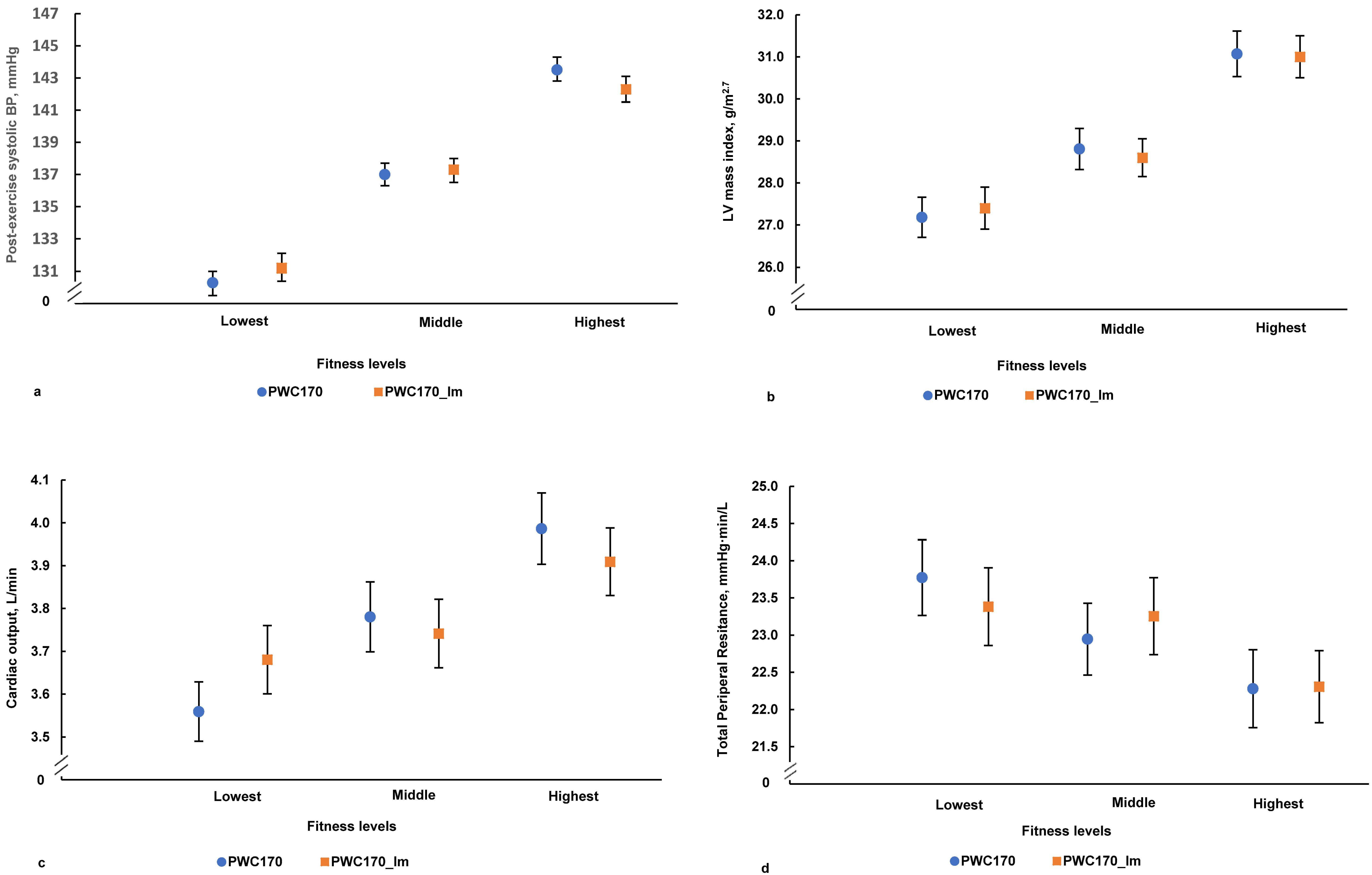
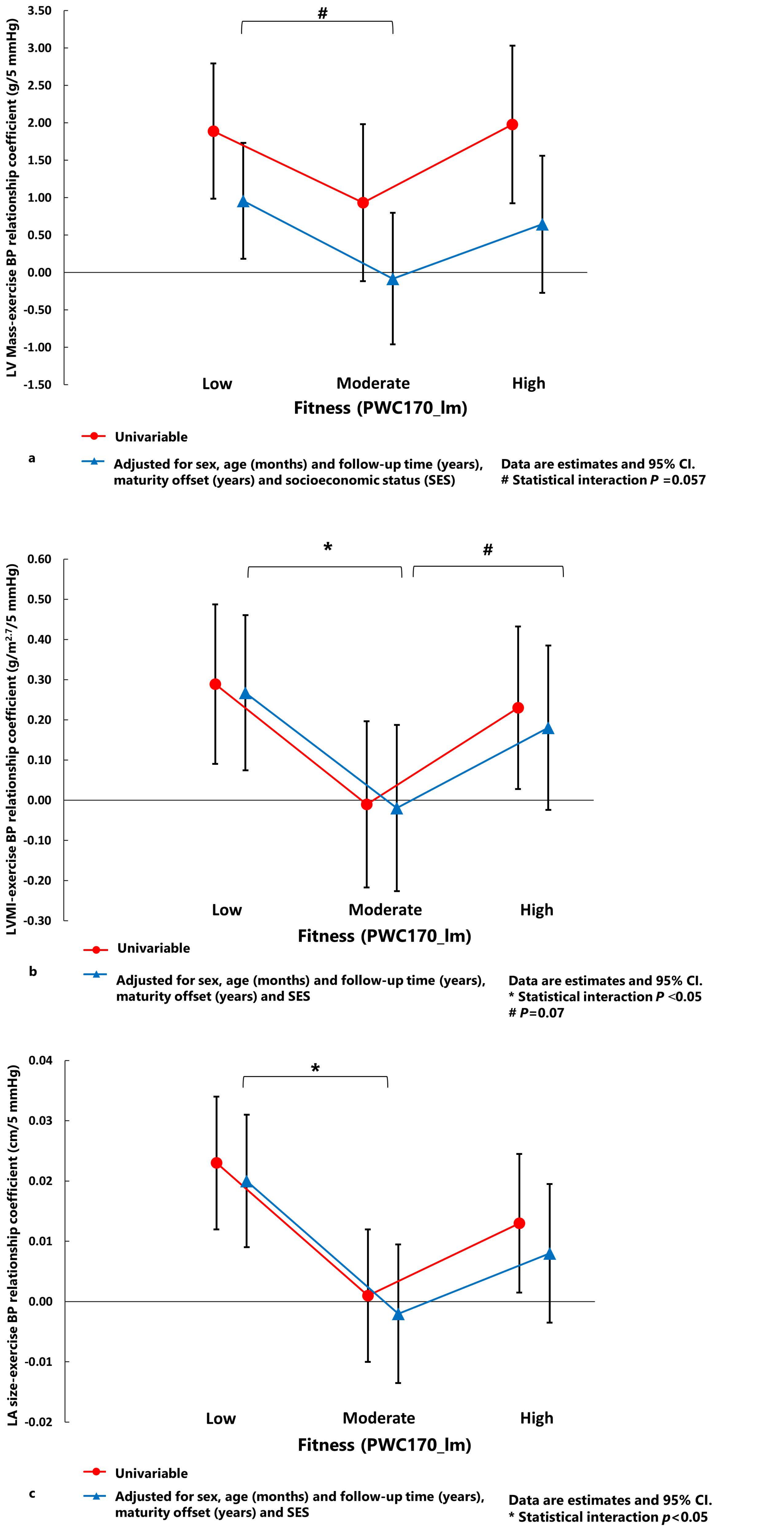


Data are estimates and 95% CI.



3.50
3.00
2.50
2.00
1.50
1.00
0.50
0.00
-0.50
-1.00
-1.50
#
LV Mass-exercise BP relationship coefficient (g/5 mmHg)
Low
Moderate
High
Fitness (PWC170_lm)
Univariable
a
Adjusted for sex, age (months) and follow-up time (years), maturity offset (years) and socioeconomic status (SES)
Data are estimates and 95% CI.
Statistical interaction P =0.057
0.60
0.50
0.40
0.30
0.20
0.10
0.00
-0.10
-0.20
-0.30
*
#
LVMI-exercise BP relationship coefficient (g/m2.7/5 mmHg)
Low
Moderate
High
Fitness (PWC170_lm)
Univariable
b
Adjusted for sex, age (months) and follow-up time (years), maturity offset (years) and SES
Data are estimates and 95% CI.
* Statistical interaction P <0.05
# P=0.07
0.04
0.03
0.02
0.01
0.00
-0.01
-0.02
*
LA size-exercise BP relationship coefficient (cm/5 mmHg)
Low
Moderate
High
Fitness (PWC170_lm)
Univariable
c
Adjusted for sex, age (months) and follow-up time (years), maturity offset (years) and SES
Data are estimates and 95% CI.
* Statistical interaction p<0.05

Table 1. Baseline demographic and clinical characteristics, body composition and exercise parameters by fitness levels

	Fitness level			
	Lowest	**Middle**	**Highest**	**Combined**
a. Demographic /Clinical				
Age, years (n=4659)	15.4 (0.3)	15.4 (0.3)	15.4 (0.3)	15.4 (0.3)
Male, percentage (n=4657)	331 (21.3%)	772 (49.7%)	1,187 (76.5%)	2290 (49.2%)
Cholesterol, mmol/l (n=2974)	3.9 (0.7)	3.7 (0.6)	3.6 (0.6)	3.7 (0.6)
*Triglycerides, mmol/l (n=2974)	0.9 (0.4)	0.8 (0.3)	0.8 (0.3)	0.8 (0.4)
Glucose, mmol/l (n=2861)	4.3 (0.3)	4.3 (0.3)	4.4 (0.3)	4.3 (0.3)
HDL, mmol/l (n=2974)	1.3 (0.3)	1.3 (0.3)	1.3 (0.3)	1.3 (0.3)
LDL, mmol/l (n=2974)	2.2 (0.6)	2.1 (0.5)	2.0 (0.5)	2.1 (0.6)
b. Body Composition				
Height, m (n=4657)	1.7 (0.1)	1.7 (0.1)	1.7 (0.1)	1.7 (0.1)
Weight, kg (n=4654)	59.1 (11.8)	61.7 (11.5)	64.2 (11.3)	61.7 (11.7)
Body mass index, kg/m^2 (n=4654)	21.3 (3.7)	21.4 (3.6)	21.5 (3.2)	21.4 (3.5)
Total fat mass, kg (n=4659)	17.3 (9.0)	15.5 (9.6)	13.0 (8.6)	15.3 (9.2)
Total lean mass, kg (n=4659)	38.7 (6.4)	43.2 (7.6)	48.2 (8.1)	43.4 (8.3)
c. Pre-exercise (resting) BP Parameters				
Pre-exercise SBP, mm Hg (n=4657)	122 (11)	123 (11)	124 (11)	123 (11)
Pre-exercise DBP, mm Hg (n=4657)	67 (9)	67 (9)	68 (9)	68 (9)
Pre-exercise HR, bpm (n=4652)	81 (12)	74 (11)	67 (11)	74 (12)
d. Exercise Test Parameters				
Post-exercise SBP, mm Hg (n=4659)	131 (16)	137 (15)	142 (15)	137 (16)
Post-exercise DBP, mm Hg (n=4659)	60 (11)	58 (11)	57 (11)	58 (11)
Post-exercise HR, bpm (n=4657)	131 (12)	124 (13)	113 (15)	123 (15)
Peak workload, watts (n=4659)	84 (18)	121 (25)	164 (32)	123 (41)
Peak HR, bpm (n=4659)	169 (7)	167 (7)	162 (9)	166 (9)
e. fitness				
PWC170_lm, watts/kg (n=4659)	2.2 (0.3)	2.9 (0.2)	3.7 (0.5)	2.9 (0.7)

HDL, high-density lipoprotein; LDL, low-density lipoprotein; SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate. Data are presented as mean (SD) or n (%). * Triglycerides was presented as median (interquartile range (IQR)). Fitness levels classified as lowest (first tertile), middle (second tertile) and highest (third tertile) level of PWC170_lm.

Table 2. Post-exercise systolic BP and cardiovascular structure.

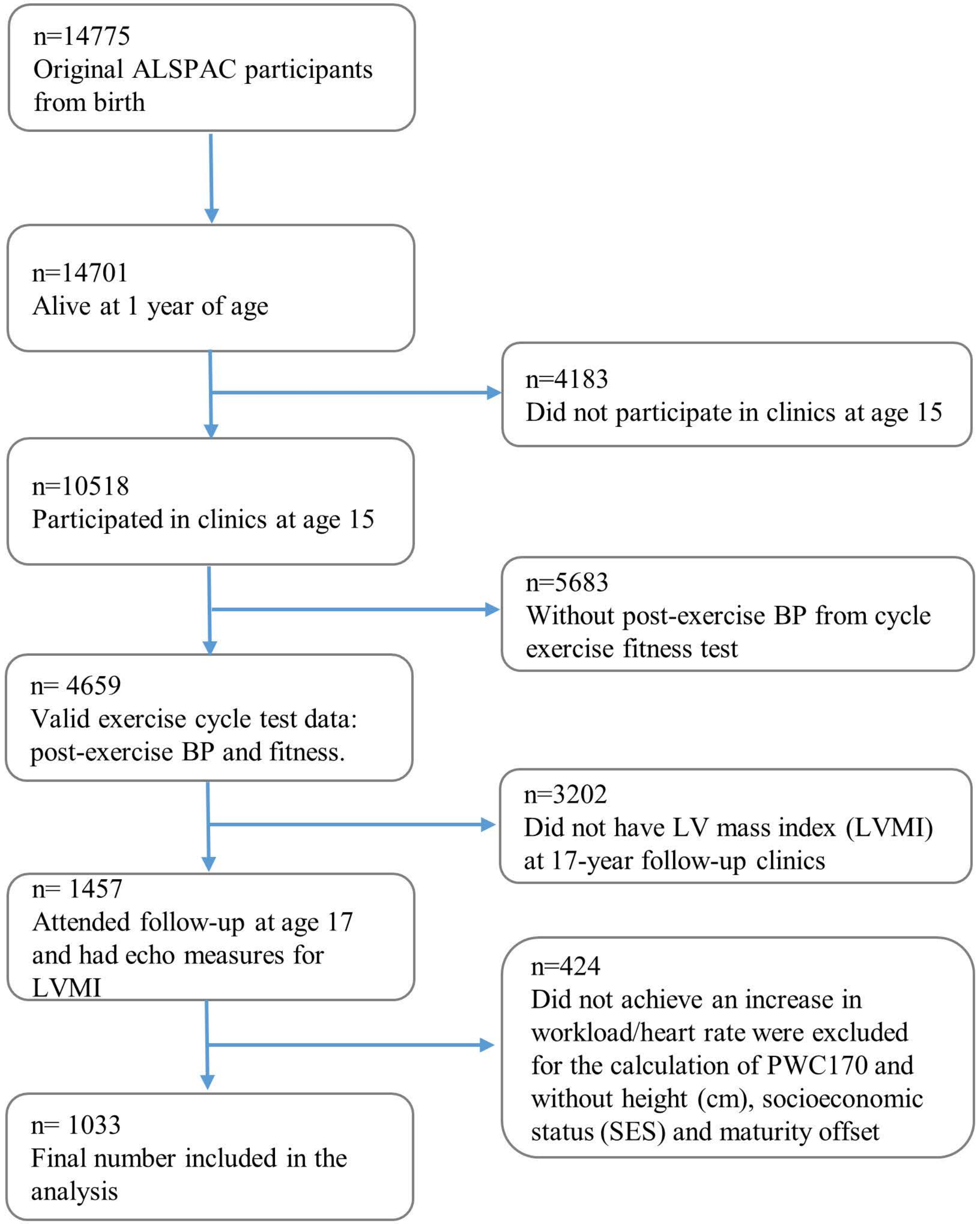
	Model 1	Model 2	Model 3	Model 4	Model 5	Model 6	Model 7
Outcome							
LV mass, g (n=1049)	2.547 (1.951, 3.142) **	0.726 (0.229, 1.224) **	0.259 (-0.221, 0.738)	0.205 (-0.252, 0.662)	-0.001 (-0.483, 0.480)	0.487 (-0.009, 0.982) †	0.106 (-0.415,0.627)
LA size, cm (n=947)	0.024 (0.016, 0.032) **	0.011 (0.003, 0.019) *	0.006 (-0.002, 0.014)	0.005 (-0.002, 0.013)	0.001 (-0.007, 0.009)	0.008 (0.0003, 0.016) *	0.002 (-0.006,0.010)
RWT (n=1049)	0.001(-0.0002, 0.002)	0.0003 (-0.0007, 0.0013)	0.0005 (-0.0005, 0.0016)	0.0005 (-0.0006, 0.0016)	-0.0001 (-0.0012, 0.0010)	0.0005 (-0.0005, 0.0015)	-0.0001 (-0.0012, 0.0010)
LV mass index, g/m$^{2.7\#}$ (n=1033)	0.273(0.159, 0.388) **	0.198 (0.081, 0.315) *	0.083 (-0.029, 0.195)	0.066 (-0.039, 0.171)	0.005 (-0.105, 0.116)	0.140 (0.024, 0.256) *	0.034 (-0.088,0.155)

Results are unit change β (95% CI) in outcome per 5 mmHg increment in post-exercise systolic BP. LV mass, left-ventricular mass; LV mass index, left-ventricular mass index; LA, left-atrial; RWT, relative wall thickness. **Model 1** – univariable; **Model 2** – model 1 plus adjustment for age (years), sex, follow-up time (years), height (cm), maturity offset and SES; **Model 3** – model 2 plus adjustment for PWC170; **Model 4** – model 3 plus adjustment for total lean body mass (g); **Model 5** – model 4 plus adjustment for pre-exercise (resting) systolic BP; **Model 6** – model 2 plus adjustment for PWC170_lm; **Model 7** – model 6 plus adjustment for pre-exercise (resting) systolic BP. *P <0.05, **P ≤0.001, † P =0.054. # Models do not include height. n values differ due to complete case analysis.

Table 3. Post-exercise systolic BP and cardiac structure (sex-pooled analyses) by fitness levels.

Fitness variables		**PWC170**			**PWC170_lm***		
Outcome		**Lowest:**	**Middle:**	**Highest:**	**Lowest:**	**Middle:**	**Highest:**
LV mass, g (n=1049)	**Univariate**	1.097 (0.309, 1.885) n=364*	0.711 (-0.192, 1.613) n=349	0.795 (-0.219, 1.809) n=336	1.890 (0.986, 2.794) n=346**	0.933 (-0.114, 1.981) n=365	1.978 (0.924, 3.032) n=338**
	Model 1#	0.587 (-0.092, 1.266) n=364	-0.207 (-1.009, 0.596) n=349	0.460 (-0.438, 1.358) n=336	0.959 (0.185, 1.733) n=346*	-0.081 (-0.961, 0.799) n=365	0.645 (-0.269, 1.559) n=338
	Model 2#	0.218 (-0.515, 0.950) n=364	-0.275 (-1.138, 0.587) n=349	0.358 (-0.558, 1.274) n=336	0.445(-0.397, 1.287) n=346	-0.184 (-1.107, 0.739) n=365	0.188 (-0.758, 1.134) n=338
LV mass index, $g/m^{2.7\dagger}$ (n=1033)	**Univariate**	0.218 (0.021, 0.415) n=359*	0.076 (-0.124, 0.277) n=343	0.103 (-0.109, 0.315) n=331	0.289 (0.090, 0.487) n=341*	-0.010 (-0.217, 0.197) n=358	0.230 (0.028, 0.432) n=334*
	Model 1	0.193 (0.007, 0.379) * n=359	0.068 (-0.128, 0.264) n=343	0.124 (-0.079, 0.328) n=331	0.267 (0.074, 0.461) n=341*	-0.019 (-0.226, 0.187) n=358	0.181 (-0.024, 0.385) n=334*
	Model 2	0.050 (-0.149, 0.248) n=359	-0.010 (-0.222, 0.202) n=343	0.073 (-0.133, 0.279) n=331	0.107 (-0.103, 0.316) n=341	-0.069 (-0.287, 0.148) n=358	0.070 (-0.141, 0.281) n=334
LA size, cm (n=947)	**Univariate**	0.017 (0.004, 0.030) n=323*	0.010 (-0.004, 0.023) n=309	0.006 (-0.009, 0.021) n=315	0.027 (0.013, 0.040) n=306**	0.003 (-0.011, 0.017) n=332	0.013 (-0.002, 0.027) n=309*
	Model 1	0.012 (-0.0003, 0.024) n=323&	0.002 (-0.011, 0.015) n=309	0.004 (-0.010, 0.019) n=315	0.019 (0.006, 0.032) n=306*	-0.001 (-0.015, 0.013) n=332	0.006 (-0.009, 0.020) n=309
	Model 2	0.007 (-0.006, 0.021) n=323	0.001 (-0.013, 0.015) n=309	0.0001 (-0.014, 0.015) n=315	0.013 (-0.002, 0.027) n=306	-0.007 (-0.022, 0.007) n=332	-0.001 (-0.016, 0.014) n=309
RWT (n=1049)	**Univariate**	0.002 (-0.0003, 0.004) n=364	0.001 (-0.001, 0.002) n=349	-0.0002 (-0.002, 0.002) n=336	0.001 (-0.001, 0.003) n=346	0.001 (-0.001, 0.003) n=365	0.0006 (-0.001, 0.002) n=338
	Model 1	0.001 (-0.001, 0.003) n=364	0.0001 (-0.002, 0.002) n=349	-0.0004 (-0.002, 0.001) n=336	0.001 (-0.001, 0.003) n=346	0.0005 (-0.001, 0.002) n=365	0.0003 (-0.001, 0.002) n=338
	Model 2	0.0002 (-0.002, 0.002) n=364	-0.0002 (-0.002, 0.002) n=349	-0.0007 (-0.003, 0.001) n=336	-0.0002 (-0.002, 0.002) n=346	-0.0001 (-0.002, 0.002) n=365	-0.0001 (-0.002, 0.002) n=338

Results are unit change β (95% CI) in outcome per 5 mmHg increment in post-exercise systolic BP. LV, left-ventricular; LA, left-atrial; RWT, relative wall thickness. # Model 1: adjusted models include sex, age (months), follow-up time (years), SES, lean body mass (g), height (cm) and maturity offset. Model 2: adjusted model includes sex, age (months), follow-up time (years), SES, lean body mass (g), height (cm), maturity offset and pre-exercise (resting) systolic BP. *Model 1 and model 2 do not include lean body mass (g). † Model 1 and model 2 do not include height (cm). & P =0.056 *P < 0.05, **$P \leq 0.001$.


n=14775
Original ALSPAC participants from birth
n=14701
Alive at 1 year of age
n=4183
Did not participate in clinics at age 15
n=10518
Participated in clinics at age 15
n=5683
Without post-exercise BP from cycle exercise fitness test
n= 4659
Valid exercise cycle test data: post-exercise BP and fitness.
n=3202
Did not have LV mass index (LVMI) at 17-year follow-up clinics
n= 1457
Attended follow-up at age 17 and had echo measures for LVMI
n=424
Did not achieve an increase in workload/heart rate were excluded for the calculation of PWC170 and without height (cm), socioeconomic status (SES) and maturity offset
n= 1033
Final number included in the analysis

ONLINE SUPPLEMENT

The influence of fitness on exercise blood pressure and its association with cardiac structure in adolescence.

Zhengzheng Huang[1], Ricardo Fonseca,[1] James E. Sharman,[1] Chloe Park,[2] Nish Chaturvedi,[2, 3] Laura D. Howe,[4] Alun D. Hughes,[2, 3] & Martin G. Schultz.[1]

1) Menzies Institute for Medical Research, University of Tasmania, Hobart, Australia
2) Department of Population Science and Experimental Medicine, Institute of Cardiovascular Science, University College London, London, UK.
3) MRC Unit for Lifelong Health and Ageing at UCL, London, UK
4) MRC Integrative Epidemiology Unit, University of Bristol, Bristol, UK

Corresponding author:
Dr Martin G. Schultz
Menzies Institute for Medical Research, College of Health and Medicine,
University of Tasmania, Hobart, 7000, Australia
Telephone: +61 (0) 3 6226 4264
Fax: +61 (0) 3 6226 7704
Email: Martin.Schultz@utas.edu.au

Supplemental Table S1. Baseline characteristics of study participants with and without echocardiography at follow-up

	mean (SD) or n (%)	with echo measurements	without echo measurements	*P*
a. Demographic /Clinical				
Age, years (n=4837)	15.4 (0.3)	15.4 (0.3)	15.4 (0.3)	0.11
Male, percentage (n=4835)	2350 (48.6%)	779 (46.8%)	1571 (49.5%)	0.07
Cholesterol, mmol/l (n=3077)	3.8 (0.6)	3.8 (0.7)	3.8 (0.6)	0.99
*Triglycerides, mmol/l (n=3077)	0.8 (0.4)	0.7 (0.4)	0.8 (0.4)	0.62
Glucose, mmol/l (n=2960)	4.3 (0.3)	4.3 (0.3)	4.3 (0.3)	0.46
HDL, mmol/l (n=3077)	1.3 (0.3)	1.3 (0.3)	1.3 (0.3)	0.33
LDL, mmol/l (n=3077)	2.1 (0.6)	2.1 (0.6)	2.1 (0.5)	0.60
b. Body Composition				
Height, m (n=4801)	1.7 (0.1)	1.7 (0.1)	1.69 (0.1)	0.43
Weight, kg (n=4793)	61.6 (11.7)	61.4 (11.2)	61.6 (12.0)	0.50
Body mass index, (n=4793)	21.4 (3.5)	21.4 (3.4)	21.4 (3.6)	0.89
Total fat mass, kg (n=4761)	15.3 (9.2)	15.3 (8.9)	15.3 (9.3)	0.92
Total lean mass, kg (n=4761)	43.3 (8.4)	43.1 (8.3)	43.4 (8.4)	0.35
c. Clinic BP Parameters				
Clinic SBP, mm Hg (n=4835)	123 (11)	123 (11)	123 (11)	0.94
Clinic DBP, mm Hg (n=4835)	68 (9)	68 (9)	68 (9)	0.73
Clinic HR, bp/min (n=4830)	74 (12)	74 (12)	74 (12)	0.39
d. Exercise Test Parameters				
Post-exercise SBP, mm Hg (n=4837)	137 (16)	137 (16)	137 (16)	0.47
Post-exercise DBP, mm Hg (n=4837)	58 (11)	58 (11)	58 (11)	0.64
Post-exercise heart rate, bpm (n=4835)	123 (16)	123 (15)	123 (16)	0.30
Peak workload, watts (n=4837)	122 (41)	123 (41)	122 (42)	0.59
Peak heart rate, bpm (n=4837)	165 (9)	166 (9)	165 (9)	0.06
e. fitness				
PWC170, watts (n=4732)	130.4 (48.0)	129.0 (48.1)	129.6 (48.8)	0.66
PWC170_lm, watts/kg (n=4659)*	3.0 (0.7)	3.0 (0.7)	3.0 (0.7)	0.76

HDL: high-density lipoprotein. LDL: low-density lipoprotein. SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate. Data are presented as mean (SD) or n (%). * Triglycerides was presented as median (interquartile range (IQR)) and Kruskal-Wallis H test was performed for comparison.

Supplemental Table S2. Lean body mass and its correlation with fitness and cardiac structure.

	Lean body mass, g	PWC170, watts	LV mass, g	LV mass index, g/m$^{2.7}$	LA size, cm
Lean body mass, g	1.000				
PWC170, watts	0.809	1.000			
LV mass, g	0.686	0.616	1.000		
LV mass index, g/m$^{2.7}$	0.286	0.312	0.819	1.000	
LA size, cm	0.392	0.364	0.542	0.478	1.000

P values for all Pearson's correlations were <0.001.

Supplemental Table S3. BMI and its correlation with fitness and cardiac structure.

	Body mass index, kg/m^2	PWC170, watts	PWC170_lm, watts/kg	LV mass, g	LV mass index, g/m$^{2.7}$	LA size, cm
Body mass index, kg/m^2	1.000					
PWC170, watts	0.106	1.000				
PWC170_lm, watts/kg	0.021*	0.875	1.000			
LV mass, g	0.304	0.616	0.410	1.000		
LV mass index, g/m$^{2.7}$	0.456	0.312	0.261	0.819	1.000	
LA size, cm	0.394	0.364	0.263	0.542	0.478	1.000

P values for all Pearson's correlations were <0.001 Except for * *P*=0.148

Supplemental Table S4. Interaction of PWC170_lm tertiles with post-exercise systolic BP on cardiac structure.

		Model 1		**Model 2**		**Model 3**	
Outcome	**PWC170_lm**	**β (95% CI) per 5 mmHg of post-exercise systolic BP**	***P* for interaction**	**β (95% CI) per 5 mmHg of post-exercise systolic BP**	***P* for interaction**	**β (95% CI) per 5 mmHg of post-exercise systolic BP**	***P* for interaction**
LV mass, g	Tertile 1	0.956 (-0.465, 2.378)	0.187	1.118 (-0.075, 2.311)	0.066	1.064 (-0.120, 2.248)	0.078
	Tertile 2	Reference		Reference		Reference	
	Tertile 3	1.045 (-0.398, 2.488)	0.156	0.942 (-0.269, 2.154)	0.127	0.981 (-0.221, 2.182)	0.110
LV mass index, g/m$^{2.7}$	Tertile 1	0.299 (0.011, 0.587)	0.042	0.296 (0.016, 0.576)	0.038	0.282 (0.006, 0.559)	0.046
	Tertile 2	Reference		Reference		Reference	
	Tertile 3	0.240 (-0.052, 0.532)	0.107	0.263 (-0.021, 0.547)	0.070	0.273 (-0.007, 0.554)	0.056
LA size, cm	Tertile 1	0.023 (0.003, 0.044)	0.022	0.024 (0.004, 0.043)	0.016	0.023 (0.004, 0.042)	0.017
	Tertile 2	Reference		Reference		Reference	
	Tertile 3	0.010 (-0.011, 0.030)	0.352	0.008 (-0.011, 0.028)	0.395	0.010 (-0.009, 0.029)	0.313

LV mass, left-ventricular mass; LV mass index, left-ventricular mass index; LA, left-atrial. **Model 1** – univariable; **Model 2** – model 1 plus adjustment for age (years), sex, follow-up time (years), height (cm) maturity offset and SES; **Model 3** – model 2 plus adjustment for pre-exercise (resting) systolic BP.